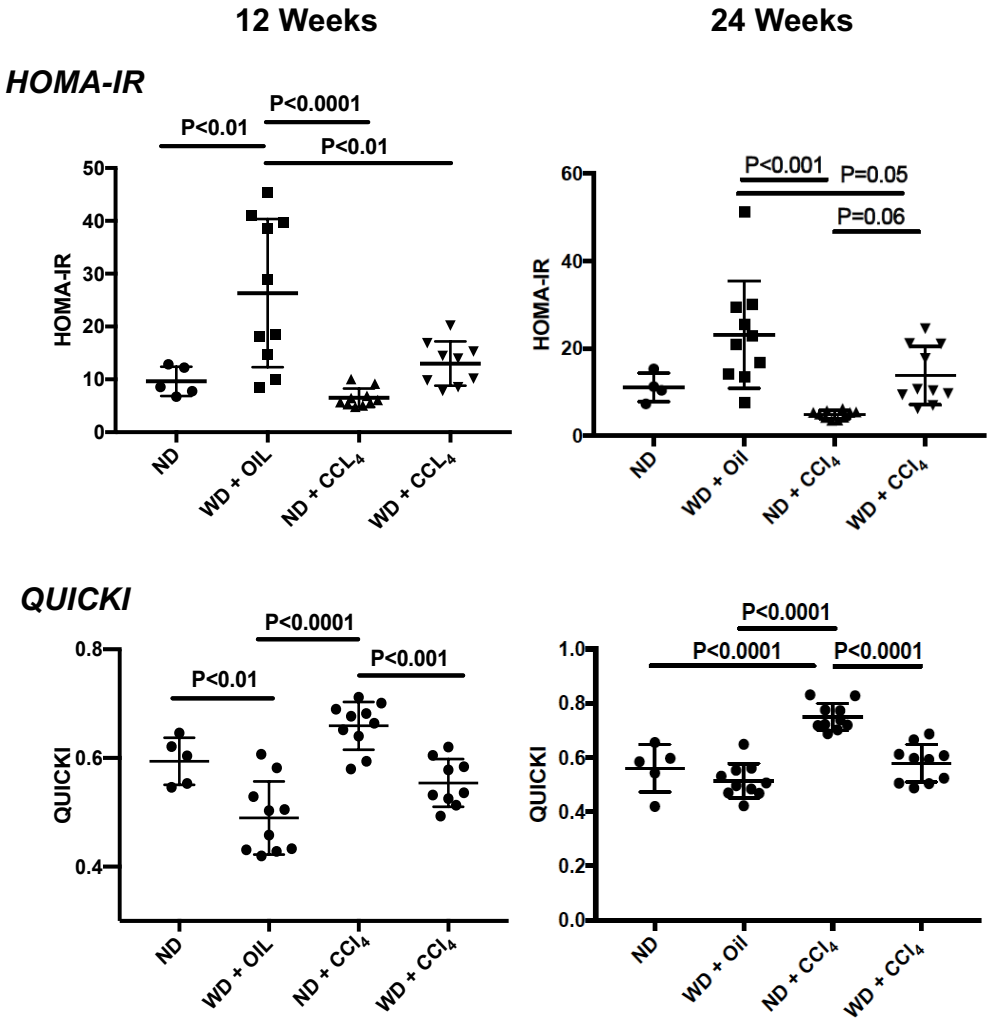
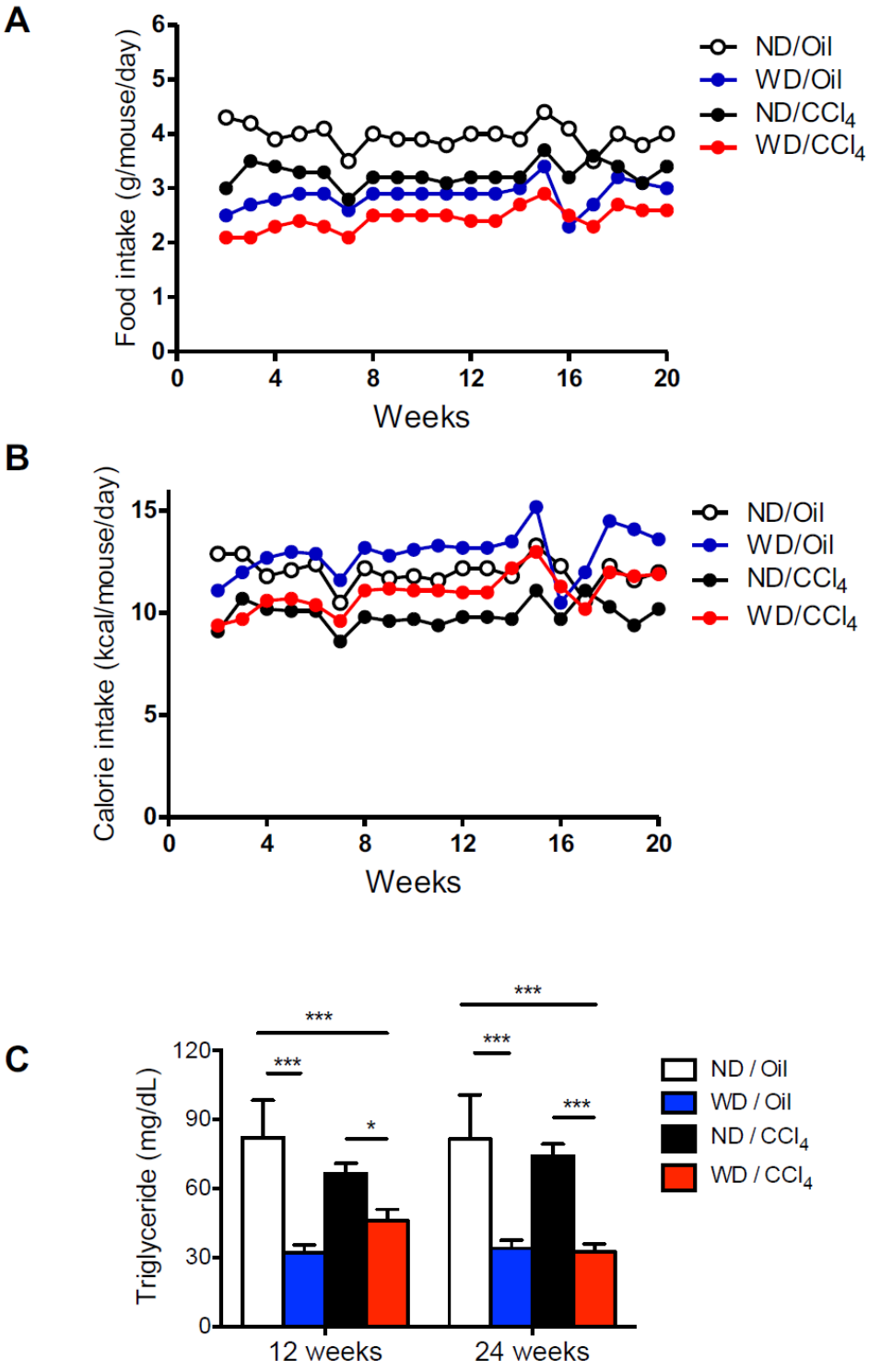


Supplementary Figure 1. HOMA IR and QUICKI Assessments of Insulin Resistance.

HOMA IR and QUICKI were calculated using a correction for mice as previously described [14,15]. Both indices demonstrate increased insulin resistance in mice fed a Western Diet, which was partially attenuated when CCl_4 was added.

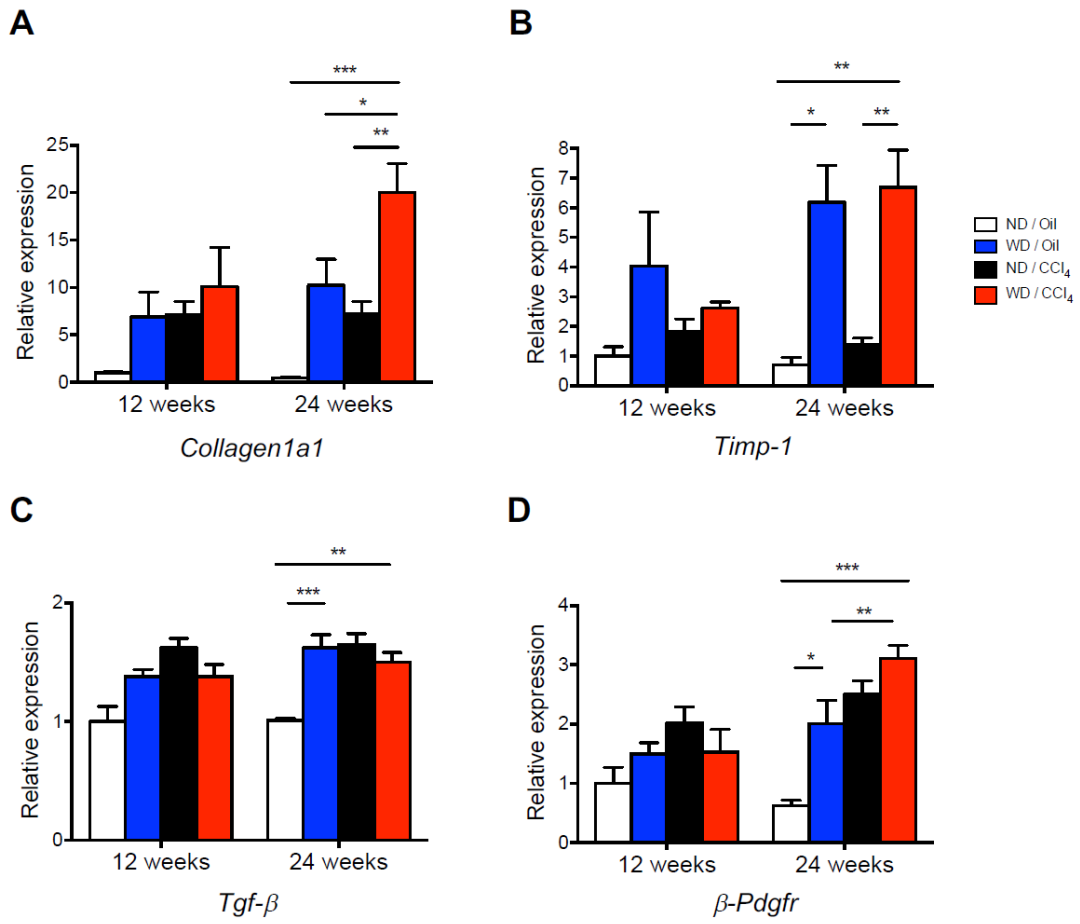


Supplementary Figure 2. Daily food and calorie intake and serum triglyceride levels

(A) Food intake was measured per cage and shown as daily food intake per mouse.

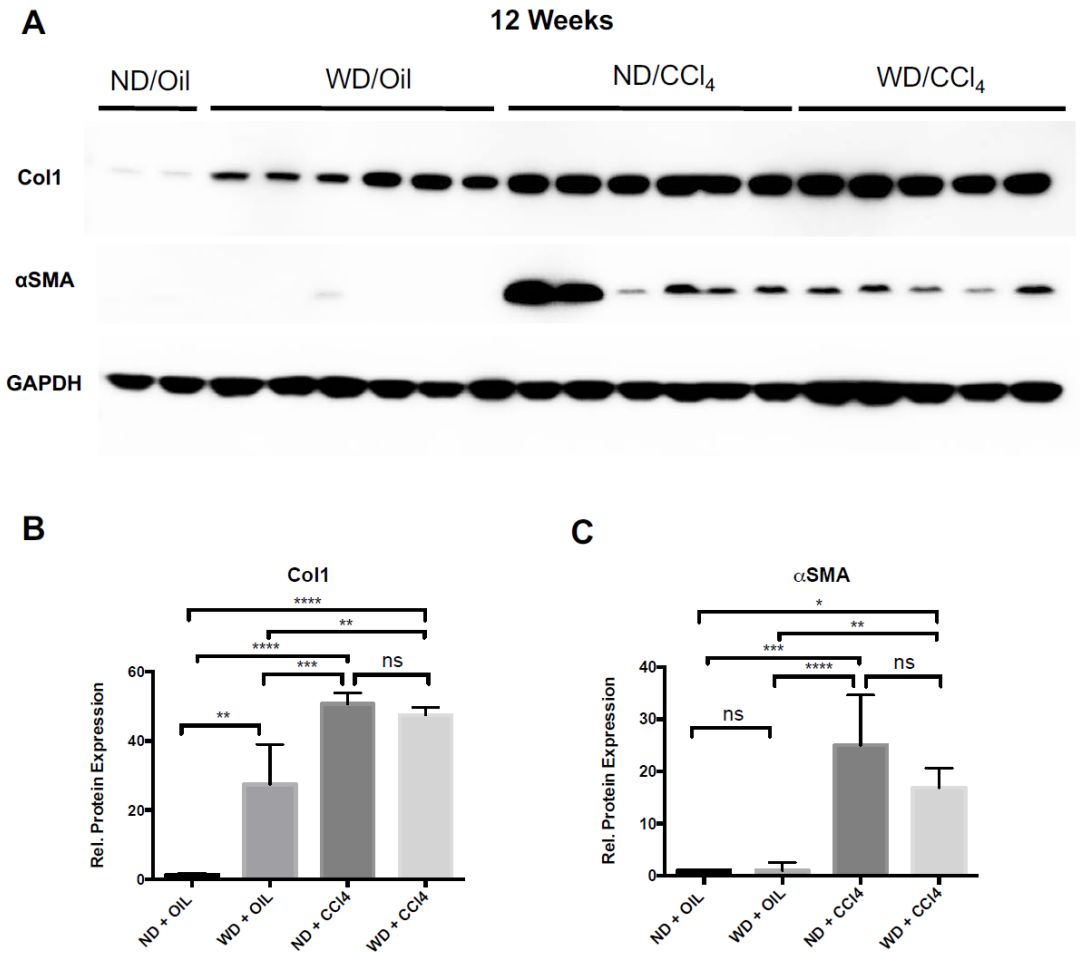
(B) Daily calorie intake per mouse was calculated based on daily food intake (ND: 3.04 kcal/g and WD: 4.5 kcal/g). Data are expressed as mean.

(C) Serum triglyceride was measured at 12 and 24 weeks. ND/Oil: n = 5, WD/Oil: n = 10, ND/CCl_4: n = 10, WD/CCl_4: n = 9 at 12 weeks, ND/Oil: n = 5, WD/Oil: n = 10, ND/CCl_4: n = 10, WD/CCl_4: n = 10 at 24 weeks. Results were expressed as mean ± SEM, and were compared by two-way ANOVA with Bonferroni post-hoc test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.



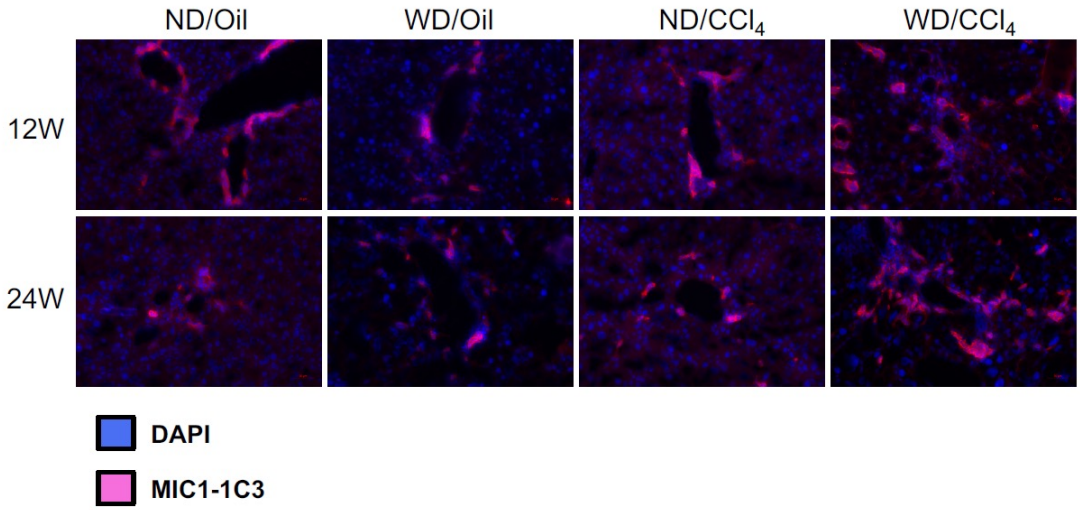
Supplementary Figure 3. Quantitative PCR for fibrogenic genes in mice treated with diet and CCl_4

Quantitative RT-PCR for fibrogenic genes including *Collagen 1α1* (A), *Timp-1* (B), *Tgf-β* (C), and *β-Pdgfr* (D). Data was normalized to *Gapdh* and to control group (ND/Oil). Results were expressed as mean ± SEM, and were compared by two-way ANOVA with Bonferroni post-hoc test. ND/Oil: n = 3, WD/Oil: n = 5-8, ND/CCl_4: n = 5-6, WD/CCl_4: n = 5-10 at 12 and 24 weeks. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

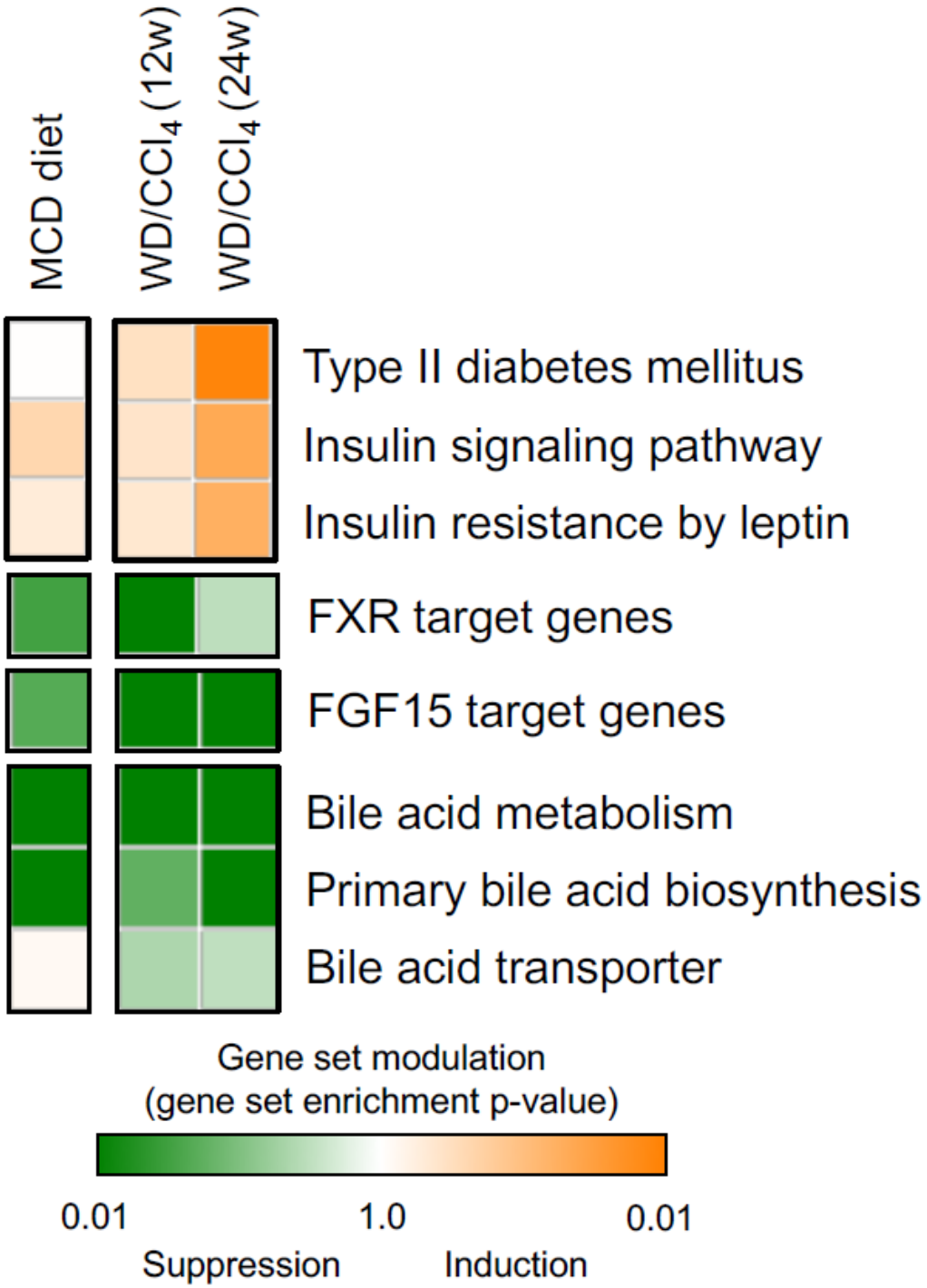


Supplementary Figure 4. Whole liver protein expression of Collagen 1 and αSMA.

Whole liver lysates from control animals treated with either ND/Oil or ND/CCl_4, and animals treated with WD/Oil or WD/CCl_4 were analyzed by immunoblotting for Collagen 1, αSMA and Gapdh (A). Normalized densitometric quantification of the band intensities are depicted in the bar graphs below the blot (B, C). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

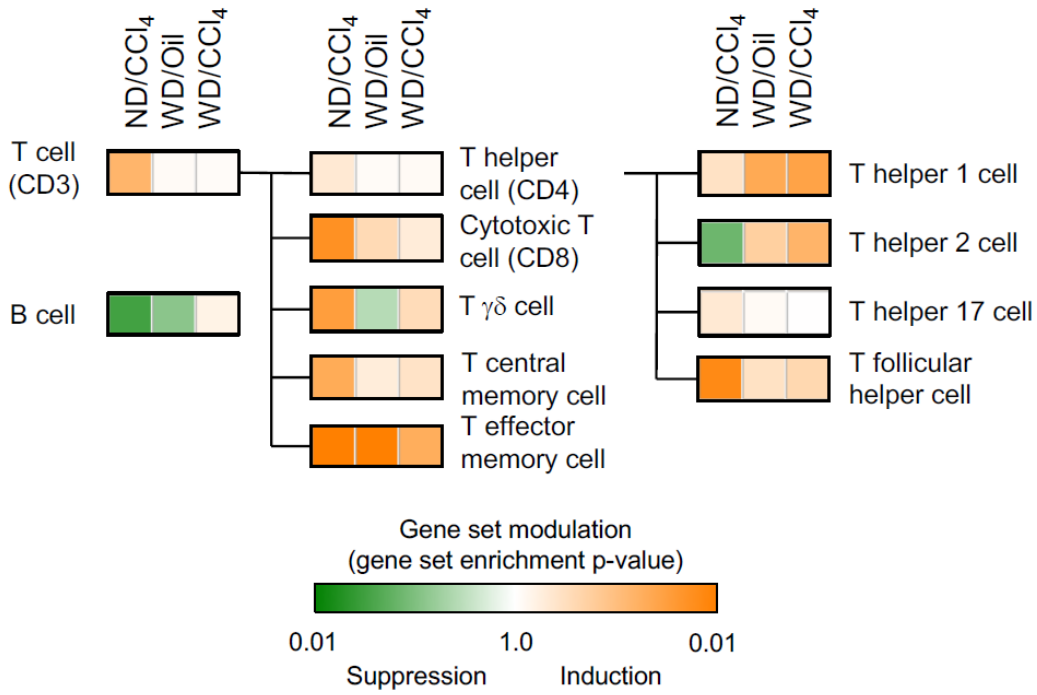


Supplementary Figure 5. Expansion of MIC-1C3 positive cells in WD/CCl_4 liver. Immunostaining for MIC1-1C3, a hepatic progenitor cell marker[53], was performed on liver sections from representative mice treated with ND/Oil, WD/Oil, ND/CCl4, and WD/CCl4 for 12 and 24 weeks. (Original magnification x 200).



Supplementary Figure 6. Transcriptomic dysregulation of insulin/diabetes- and cholesterol metabolism-related pathways and therapeutically targetable pathways in the MCD diet model compared to the WD/CCl_4 model.

Transcriptomic dysregulation of insulin/diabetes- and cholesterol metabolism-related pathways (Supplementary Table 1) were assessed in a MCD diet model and our high fructose cholesterol supplemented (WD/CCl_4, 12 weeks and 24 weeks) mouse models using GSEA. For candidate NASH therapeutic target pathways, transcriptional target gene sets (FXR target genes, FGF15 target genes) were generated from publicly available transcriptome datasets (Supplementary Table 5 as the top 100 differentially expressed genes by random permutation-based *t*-test. Also, transcriptomic dysregulation of bile acid-related pathways (Supplementary Table 1) was analyzed. MCD: methionine- and choline-deficient, GSEA: gene set enrichment analysis.



Supplementary Figure 7. Induction of immune cell subset gene signatures in WD/ CCl_4 mouse models.

Induction of immune cell subset gene signature[54] was evaluated in our ND/CCL_4 AND WD +/- CCl_4 mouse models using GSEA. MCD: methionine- and choline-deficient, WD/CCl_4: high fat/cholesterol diet, CCl_4: carbon tetrachloride, GSEA: gene set enrichment analysis.

Supplementary Table 1. Insulin/diabetes-, cholesterol metabolism- and bile acid-related pathways

Description	Gene set from MSigDB
Insulin/diabetes-related pathways	
Type II diabetes mellitus	KEGG_TYPE_II_DIABETES_MELLITUS
Insulin signaling pathway	KEGG_INSULIN_SIGNALING_PATHWAY
Insulin resistance by leptin	BIOCARTA_LEPTIN_PATHWAY
Bile acid-related pathways	
Bile acid metabolism	HALLMARK_BILE_ACID_METABOLISM
Primary bile acid biosynthesis	KEGG_PRIMARY_BILE_ACID_BIOSYNTHESIS
Bile acid transporter	REACTOME_BILE_SALT_AND_ORGANIC_ANION_SLC_TRANSPORTERS

MSigDB: Molecular Signature Database (www.broadinstitute.org/msigdb).

Supplementary Table 2. Previously published diet, chemical, and/or genetic NASH mouse models for transcriptomic analysis

Title	Strain	Model type	Diet duration	High fat	High cholesterol	High sugar	Dataset accession number	Reference
HFChSuD #1	C57BL/6	Diet	20 weeks	Yes	Yes	Yes	GSE38141	*Mol Nutr Food Res* 2011:55;530-40
HFChSuD #2	C57BL/6	Diet	12 weeks	Yes	Yes	Yes	GSE52748	*Lab Invest* 2014:94;394-408
HFChSuD #3	B6/129	Diet	52 weeks	Yes	Yes	Yes	GSE67680	*J Hepatol* 2016:65;579-88
HFChD #1	C57BL/6	Diet	16 weeks	Yes	Yes	No	GSE38013	*Hepatology* 2014:59;1750-60
HFChD #2	C57BL/6	Diet	24 weeks	Yes	Yes	No	GSE39549	*BMC Genomics* 2012:13;450
HFD	C57BL/6	Diet	36 weeks	Yes	No	No	GSE59042	*Int J Biochem Cell Biol* 2015:64;265-76
MCD+HFD	C57BL/6	Diet	8 weeks	Yes	No	No	GSE35961	*PLoS One* 2012:7;e43056
WSB/EiJ CFD	WSB/EiJ	Diet	12 weeks	No	No	No	GSE62362	*FASEB J* 2012:26:4592-602
C3H/HeJ CFD	C3H/HeJ	Diet	12 weeks	No	No	No	GSE62362	*FASEB J* 2012:26;4592-602
A/J CFD	A/J	Diet	12 weeks	No	No	No	GSE62362	*FASEB J* 2012:26;4592-602
Pten KO	C57BL/6	Genetic	60 weeks	No	No	No	GSE70681	NA
Gnmt KO	C57B6SJL	Genetic	32 weeks	No	No	No	GSE63027	*PLoS One* 2015:10;e0124544
Mat1a KO	C57B6SJL	Genetic	32 weeks	No	No	No	GSE63027	*PLoS One* 2015:10;e0124544
Mir122 KO	B6/129	Genetic	8 weeks	No	No	No	GSE27713	*J Clin Invest* 2012:122;2884-97
ob/ob	C57BL/6J	Genetic	3 weeks	No	No	No	GSE22608	*PLoS One* 2010:5;e13858
STAM	C57BL/6J	Chemical+diet	20 weeks	No	No	No	GSE83596	NA

HFChSuD: high fat/cholesterol/sugar diet, HFCh: high fat/cholesterol diet, HFD: high fat diet, MCD, methionine/choline-deficient: CFD, choline/folate-deficient, GSE: NCBI Gene Expression Omnibus database (www.ncbi.nlm.nih.gov/geo) dataset accession number.

Supplementary Table 3. CD3, CD4, CD8 cell numbers in Normal and WD/CCl_4 Mice at 12 weeks

Condition	$CD3^+$ cells /hpf	$CD4^+$ cells /hpf	$CD8^+$ cells/hpf
Normal Diet + Vehicle	100 (2.9)	19 (1.2)	15 (0.8)
Western Diet + CCl_4	283 (5.9) ***	120 (3.2) ***	108 (3.3) ***

Date are expressed as mean (± SEM). High-powered field (hpf) 20 fields at 400X magnification. *** $P < 0.001$.

Supplementary Table 4. Induction of human HCC subclass signature genes in HCC developed in WD + CCl_4 mice

Human HCC subtype	Signature genes	NES	p	FDR
S2	Upregulated genes	2.34	<0.001	<0.001
	Downregulated genes	-2.22	<0.001	<0.001
S1	Upregulated genes	2.04	<0.001	<0.001
	Downregulated genes	-2.03	<0.001	<0.001
S3	Upregulated genes	1.94	<0.001	<0.001
	Downregulated genes	-2.04	<0.001	<0.001

Supplementary Table 5. Publicly available datasets used to generate transcriptional target gene sets

Signature	First author	Pubmed ID	Dataset accession number	Reference
FXR target genes	Zhan L	25198545	GSE54557	*PLoS One* 2014;9(9):e105930
FGF15 target genes	Potthoff MJ	21641554	GSE29426	*Cell Metab* 2011 Jun 8;13(6):729-38

FXR: Farnesoid X receptor, FGF: fibroblast growth factor, GSE: NCBI Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo/) dataset accession number.